



**TITLE:** Long-term Use of Ondansetron, Dolasetron and Granisetron for the Prevention of Nausea and Vomiting: A Review of the Clinical Effectiveness and Safety

**DATE:** 23 April 2014

## **CONTEXT AND POLICY ISSUES**

Nausea and vomiting are two of the most severe and distressing side effects in patients receiving chemotherapeutic drugs for cancer treatment.<sup>1</sup> Previous studies have indicated that at least 90% of patients receiving highly emetogenic chemotherapeutics such as cisplatin and paclitaxel suffer emesis if prophylactic antiemetics are not provided.<sup>2</sup> Inadequate control of nausea and vomiting in these patients may lead to reduced nutritional status, impaired health-related quality of life, or reduce adherence to treatment.<sup>3</sup> Postoperative nausea and vomiting (PONV) are common adverse events following surgery and anaesthesia, and also a frequent cause of unplanned readmission in ambulatory surgery.<sup>4</sup> Serotonin receptor antagonists (5-HT<sub>3</sub>RA) are one of the most widely used pharmacological therapy for chemotherapy-induced nausea and vomiting (CINV). First generation 5-HT<sub>3</sub>RA agents, including ondansetron, granisetron and dolasetron, in combination with a corticosteroid plus or minus a neurokinin-1 inhibitor, have been the standard of care for acute CINV prevention.<sup>1</sup> The clinical effectiveness of 5-HT<sub>3</sub>RA agents in preventing PONV has been demonstrated in clinical trials as well.<sup>5,6</sup>

Ondansetron has been approved by Health Canada in preventing CINV from both moderately and highly emetogenic chemotherapy in adults and children 4 to 12 years of age, or PONV in adults younger than 65 years of age.<sup>7,8</sup> In these patients, ondansetron is suggested to be administered up to 5 days after chemotherapy or radiotherapy, and one single dose of ondansetron is recommended in prevention of PONV.<sup>7</sup> Granisetron is indicated for prevention of CINV and radiation-induced nausea and vomiting in adults. It is administered as one single dose before initiation of chemotherapy only, or a divided dose before chemotherapy followed by a second dose 12 hours post-chemotherapy on the day when chemotherapy is given.<sup>7</sup> Granisetron is not indicated for prevention or treatment of PONV. Dolasetron tablets for oral use can be used to prevent CINV in adults; however they are contraindicated for PONV.<sup>9</sup> In 2011, Health Canada issued an alert that the injectable form of dolasetron should no longer be used to prevent CINV due to potential risk of arrhythmias.<sup>10</sup>

Effectiveness and safety of longer-term uses of ondansetron and granisetron have been

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investigated in randomized controlled trials (RCTs) enrolling patients with conditions other than nausea and vomiting, such as alcohol dependence, stable schizophrenia, and tinnitus.<sup>11-13</sup> Treatment durations ranged from 4 to 12 weeks. Treatment with these 5-HT3RAs agents was not related with higher risk of adverse events, although patients were more likely to report constipation than placebo. No serious adverse events were reported in these RCTs.

The purpose of this review is to provide evidence on the comparative clinical effectiveness and safety of the long-term use (> 5 days) of 5-HT3RAs for the prevention of nausea and vomiting.

## RESEARCH QUESTIONS

1. What is the clinical effectiveness of the long-term use (> 5 days) of ondansetron, dolasetron, and granisetron for the prevention of nausea and vomiting?
2. What is the clinical evidence on the safety and harms of the long-term use (> 5 days) of ondansetron, dolasetron, and granisetron for the prevention of nausea and vomiting?

## KEY FINDINGS

No evidence regarding the efficacy and safety of the long-term use of 5-HT3RAs in preventing nausea and vomiting was identified.

## METHODS

### Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 3), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and March 24, 2014.

### Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to the selection criteria present in Table 1.

**Table 1: Selection Criteria**

<b>Population</b>	Patients requiring anti-emetic therapy
<b>Intervention</b>	Long-term use (> 5 days) of the following 5-HT3RAs: Ondansetron, granisetron or dolasetron
<b>Comparator</b>	Other 5-HT3RAs Placebo No comparator
<b>Outcomes</b>	Decrease in nausea and vomiting Health-related quality of life Safety

**Study Designs**

Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies

5-HT3RA=5-hydroxytryptamine<sub>3</sub> receptor antagonist

**Exclusion Criteria**

Studies were excluded if they did not meet the selection criteria in Table 1, were published prior to 2009, or duplicate publications of the same study. Studies reporting short-term ( $\leq 5$  days) use of 5-HT3RA or not specifying treatment duration were excluded.

**SUMMARY OF EVIDENCE**

**Quantity of Research Available**

The literature search yielded 560 citations. Upon screening titles and abstracts, 544 citations were excluded, and 16 potentially relevant articles were retrieved for full-text review. Of the 16 potentially relevant reports, none of them met the inclusion criteria. The process of study selection is outlined in the PRISMA flowchart (Appendix 1).

Additional references of potential interest are provided in Appendix 2.

**CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING**

The research questions regarding the clinical efficacy and safety of long-term use of ondansetron, granisetron and dolasetron for preventing nausea and vomiting cannot be answered, as no evidence published within the search timeframe was identified.

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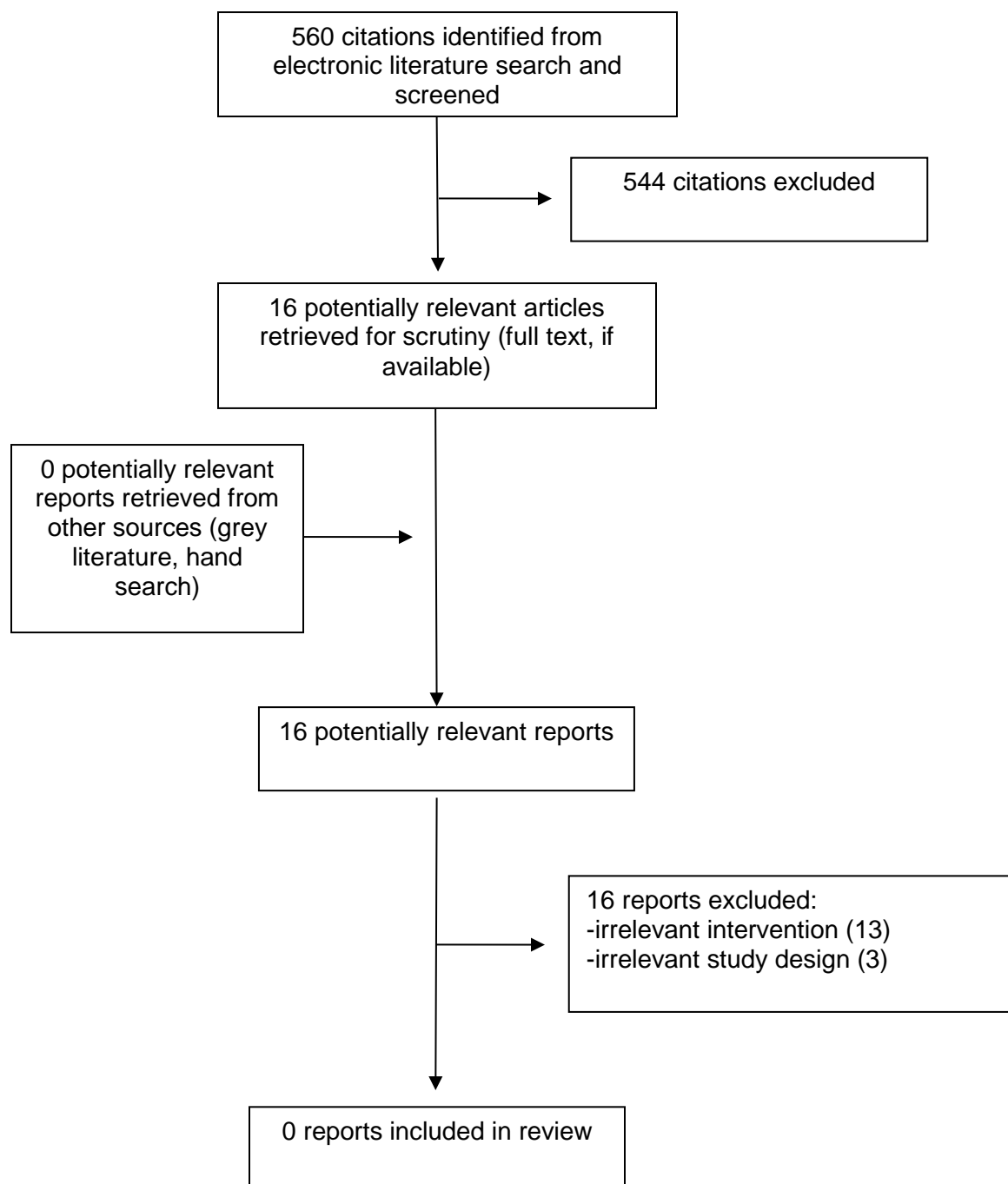
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## APPENDIX 1: Selection of Included Studies



## APPENDIX 2: Additional References of Potential Interest

### Not a systematic review

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